34. The method of claim 28, wherein the immunogenic peptide is from a cancer antigen.

35. The method of claim 28, wherein the step of contacting is carried out by administering to the patient a pharmaceutical composition comprising the immunogenic peptide.

36. The method of claim 28, wherein the step of contacting is carried out *in vitro*.

REMARKS

Status of the Application.

Claims 19-36 are added and claims 1-18 are canceled with entry of this amendment. The new claims are directed to methods of inducing an immune response against preselected antigenic determinants by contacting T cells with the peptides of claims 1-10. Support for the method claims is replete throughout the specification. Support for the terms defining the binding affinity of the claimed peptides is found in parent application 08/159,184, which is incorporated by reference in the first paragraph on page 1 of the present application. For the Examiner's convenience, copies of the relevant pages from the '184 application are attached.

On page 38, line 25, to page 39, line 24, of the '184 application, the methods by which binding affinities are determined are described. As explained there, the affinities are determined relative to a reference peptide, FLPSDYFPSV (*see*, page 39, lines 10-13). In Table 5 on page 43 and the text in the first paragraph of page 44, the categories of high, intermediate and weak binders are defined by the ratio of the apparent IC50 of the reference peptide compared to the test peptides. There, it is explained that the ratio of reference peptide IC50 to test peptide IC50 must be at least 0.01, for a peptide to be considered an intermediate or high binder. This is, of course, equivalent to describing the dissociation constant (which as explained on page 38, line 26-28, approximates IC50) of the test peptide as less than 100 times that of the reference peptide, as recited in the claims.

Applicants note with appreciation that the Examiner has withdrawn the species election of paragraph 16 in the Office Action mailed February 6, 1996, requiring applicants to elect a single peptide sequence for prosecution in this application. Thus, applicants understand that all peptides having the motifs recited above are being prosecuted in the present application. Applicants further understand that the election between motifs of 9 or 10 residues is maintained. Although applicants continue to traverse this requirement, the new claims in this application are now directed to motifs having 9 residues. Applicants understand that if both species are found to be patentable, generic claims will also be patentable.

The Invention

The present invention is based on the discovery of novel binding motifs that allow peptides to bind to HLA-A2.1 MHC products. Using these new motifs, one of skill can now screen sequences of particular protein antigens for the presence of motifs that allow peptides to bind particular A2.1 gene products. The corresponding peptides are then made and tested for their ability to bind the MHC molecules. As explained in detail below, essentially all those peptides that bind with affinity above a certain threshold are capable of inducing a CTL response against the antigen. By providing a means for identifying motif-bearing subsequences that are immunogenic, the invention greatly reduces the number of peptides to be screened for final use in treatment of disease and other uses. The methods of the invention are useful in diagnosing, preventing, or treating a number of pathological states such as viral diseases and cancers.

35 U.S.C. §101

Claims 1-10 were rejected under §101 for allegedly reading on naturally occurring peptides found on the surface of HLA-A2.1 positive cells. The pending claims are directed to use of peptides of the invention to induce cytotoxic T cell immune responses. The pending claims cannot be interpreted to read on naturally occurring peptides. Withdrawal of the rejection is respectfully requested.

35 U.S.C. §112, First Paragraph.

Claims 1-10 were rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement. In the rejection, the Examiner alleges that claims directed to "immunogenic" peptides are not enabled by the specification. In particular, the Examiner relies on two references which allegedly teach that binding to MHC is not definitive evidence that a peptide is immunogenic. In addition, the Examiner notes that the specification refers to "allele-specific" motifs, but cites references that show some peptides within the scope of the claims bind to more than one allele. These two points are addressed below.

Immunogenicity of the peptides of the invention.

The Examiner cites two papers Celis *et al.*, *Mol. Immunol.* 31:1423 (1994) and Ramensee *et al.*, *Immunogenetics* 41:178 (1995) for allegedly teaching that peptides that bind a particular MHC gene product are not necessarily immunogenic. The rejection is not apparently based on an assertion that any particular procedure required to practice the claimed methods is unpredictable or even difficult to carry out. For example, applicants do not understand the rejection to be based on an allegation that preparation of peptides, or the preparation and administration of pharmaceutical compositions containing the peptides or nucleic acids that encode them is unpredictable. Rather, the rejection is based on a concern that, if one of skill carries out these steps a useful result (*e.g.*, induction of an immune response) will not be obtained.

As explained in MPEP §2107(d), a close relationship exists between 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph. In particular, the MPEP states:

> [T]he Federal Circuit recently noted, "[o]bviously, if a claimed invention does not have utility, the specification cannot enable one to use it." *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). As such, a rejection properly imposed under 35 U.S.C. 101 should be accompanied with a rejection under 35 U.S.C. 112, first paragraph. ***It is equally clear that a rejection based on "lack of utility," whether grounded upon 35 U.S.C. 101 or 35 U.S.C. 112, first paragraph, rests on the same basis (i.e., the asserted utility is not credible)***. MPEP §2107(d) (emphasis added).

Applicants understand the rejection to be an argument that the claimed methods would not necessarily induce an immune response against the desired antigen, and thus lack a

credible utility under the patent laws. As a result, according to the Examiner, such claims are not enabled under §112, first paragraph, because undue experimentation would allegedly be required to achieve a useful result. As explained below, the underlying conclusion that a credible utility, as defined by the patent laws, has not been shown, cannot be supported after consideration of the present disclosure and the state of the art at the time of the invention.

As noted above, the pending claims are directed to peptides that have high or intermediate affinity (defined in the first paragraph of page 44, of the '184 application) for HLA-A2.1 products. As explained in the specification, a correlation exists between degree of MHC binding and immunogenicity (*see*, page 2, lines 23-27). The specification cites references, available at the time the application was filed, demonstrating that such a correlation exists. For example, Schaeffer *et al. Proc. Nat. Acad. Sci. USA* 86:4649 (1989) showed that MHC binding is related to immunogenicity. Several authors (De Bruijn et al., *Eur. J. Immunol.*, 21:2963-2970 (1991); Pamer et al., *Nature*, 353:852-955 (1991)) provided preliminary evidence that class I binding motifs can be applied to the identification of potential immunogenic peptides in animal models.

The Examiner, in contrast, relies on two references which allegedly show that no such correlation exists. As an initial matter, applicants note that both papers were published ***after*** the effective filing date of the present application. Thus, their ability to establish the state of the art ***at the time of the invention*** is questionable, at best. Applicants respectfully submit that in the absence of showing that references available at the time of the invention provide the teaching alleged to be found in these references, the rejection is improper and should be withdrawn.

Nonetheless, a careful reading of these references shows that they support, rather than refute, the conclusion that methods of the invention have a credible utility, as defined under the patent laws. For instance, the authors of the Celis *et al.* paper (including two inventors of this invention) screened the tumor associated antigen MAGE-1 using A2.1 motifs that included the motifs claimed here (*see*, Table 1). As explained on page 1427, column 1, peptides found in the initial screen were prepared and analyzed in quantitative binding assays essential identical to those used in the present invention. As explained in the second column of page 1427, peptides were divided into the same categories of high,

intermediate and weak binders as used in the present invention[1]. As can be seen in Table 3, A2.1 motif identified a total of 11 high or intermediate binders out of a total of 65 peptide identified in the protein. Since the MAGE-1 protein contains a total of 309 residues (*see*, page 1426, first column), in the absence of motifs, hundreds of peptides (all possible 9-mers and 10-mers) would have to be prepared and screened. Instead, using the motifs described in the paper, only 65 peptide were tested and the final number of candidates was then reduced to 11, based on binding.

As is evident from this paper, the authors were not identifying peptides with high affinity as an academic exercise, but because they recognized that such peptides are useful to induce immune responses against MAGE-1. As noted in the sentence bridging columns 2 and 3 of page 1427, over 90% of T cell epitopes or naturally processed peptides bind HLA molecules with an affinity of 50 nM or less. Thus, the authors reasonably concluded that those peptides showing good binding characteristics are immunogenic and are extremely likely to be used as vaccines for treatment of cancer. The Examiner quotes a section of this paper out of context to assert that the work described in this paper is not considered by the authors to be useful in the identification of immunogenic peptides. The language merely sets forth the further testing that, of course, must be carried out to definitively determine which peptides will be used for the ultimate purpose of treatment or diagnosis of disease in humans.

The language quoted from page 182 of the Rammensee *et al.* paper is also quoted out of the context. The authors state that ***historically*** binding assays have lead to obsolete results, but emphasize in the next sentence that such assays have improved. In the next section on page 182, the authors state that the main purpose for which information about binding affinities can be used is to identify T cell epitopes. The authors then describe the general approach used in the present invention to identify such peptides. Thus, applicants respectfully submit that the authors of both papers recognized the importance of motifs to

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[1] As explained on page 38, lines 10-13 of the '184 application, the average IC50 (or dissociation constant) of the reference peptide is 5nM. Since the claimed peptides (high and intermediate binders as defined on page 43of the '184 application) have a dissociation constant of less 100 times that of the reference peptide, they have a dissociation constant of 500 nM or less. This corresponds exactly to the cut-off used in the Celis *et al.* paper to identify high and intermediate binders.

define peptide antigens useful for treatment of human disease. Neither paper calls into question the value of the claimed methods for the ultimate purpose of treating or diagnosing disease in humans.

As the Examiner is undoubtedly aware, a definitive showing of human efficacy has ***never*** been required by the patent laws. To satisfy the requirements of the patent laws, an invention must have "real world" utility (*see*, MPEP §2107). As noted by the Courts:

> "practical utility" is a shorthand way of attributing 'real-world' value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public."
> *Nelson v. Bower and Crossley* 206 USPQ 206 (CCPA 1980).

Applicants respectfully submit that the motifs and methods of invention greatly simplify the identification of peptide-based vaccines and other treatments and therefore provide immediate benefit to the public. As shown above in the Celis *et al.*, without the motifs identification of such peptides requires making and screening ***every possible*** peptide sequence from a given antigen. The present invention is based on the discovery of a simple process by which only the most immunogenic peptides of a given antigen are immediately identified. The claimed methods therefore have a credible, practical utility which greatly advances the art. Nothing has been provided to show that such a utility is not sufficient to meet the requirements of the patent laws.

Applicants further respectfully submit that the Examiner's conclusory statements concerning a possible but undemonstrated lack of utility for some of the claimed peptides are insufficient as a matter of law to overcome the presumption of utility. Applicants have identified motif-bearing subsequences present in known amino acid sequences of several biologically important proteins, and synthesized these peptides. (*See*, Tables 3 and 4 of the specification.) Furthermore, Applicants have demonstrated that peptides bearing the appropriate motif both bind to the predicted class I MHC allelic products and produce cytotoxicity in CTL assays *in vitro*. (*see*, Example 10 on pages 73-77 of the '184 application). Indeed, peptides having the motif were further tested in transgenic mice expressing human HLA-A2.1 molecules. As shown in Table 23 of the '184 application, binding and

immunogenicity were closely correlated. As noted at the bottom of page 76, peptides having a binding ratio of at least 0.01 are capable of inducing CTL immune responses.

The present rejection is apparently based on a concern that a large number of possible different peptides that could fit the binding motif and that some of these might be inoperative. As noted above, the claimed methods are now directed to use of high or intermediate binding peptides. It is well settled that:

> For a proposed claim to be unpatentable, the law requires that the number of inoperable embodiments be significant in numbers and **not readily ascertained** by those of skill. *In re Cook and Merigold*, 169 U.S.P.Q. 298, 301-302 (C.C.P.A. 1971).

Applicants respectfully, submit that the instant rejection does not take into account that the specification teaches a person of ordinary skill how to readily determine which embodiments are inoperative. The specification in fact provides extensive teaching for one of skill "readily ascertain" which peptides are immunogenic. As noted above, the application teaches that there is a distinct correlation between peptide binding and immunogenicity. Applicants teach binding assays that directly measure the affinity of the peptides for a given MHC allele. Thus, one of skill using the present disclosure and methods known in the art at the time could readily ascertain peptides having the desired properties. The Examiner has not provided sufficient reason or evidence to show why the claimed methods or peptides lack utility.

Thus, for all the foregoing reasons, Applicants assert that a utility-based rejection of either the pending claims is improper, particularly in view of the amendments and additions to the claims, and they request that the § 112 rejection be withdrawn.

"Allele-specific motif"

Applicants respectfully traverse the rejection based on the assertion that the claims read on "allele-specific" motifs. Applicants note that neither the rejected claims nor the pending claims are explicitly directed to "allele-specific" motifs. Instead the claims are directed to peptides containing certain defined structural features that allow them to bind to A2.1 molecules. Nothing in the claims requires that the peptides bind these molecules exclusively. The fact that peptides that bind A2.1 molecules might also bind other alleles does

not detract from their utility in the claimed methods. In the absence of an explanation as to why such cross reactivity is detrimental to the claimed methods, the rejection should be withdrawn.

35 U.S.C. §112, second paragraph.

The rejection of claims 1-10 for allegedly being indefinite because of the term "C-terminal position" is respectfully traversed. Applicants submit that the term would be understood by those of skill to refer to the ninth residue of the motif of the immunogenic peptides. Nonetheless, to expedite prosecution of the present application, the pending claims are directed to peptides in which the recited residues occur at the "C-terminus" of the motif, thus rendering the present rejection moot. Withdrawal of the rejection is respectfully requested.

35 U.S.C. §102.

Claims 2, 4, 6 and 10 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Sette *et al. J. Immunol.* 147:3893-3900 (1991) is overcome by the new claims. New claims 27-34 are directed to methods using peptide having the same motif as the rejected claims. The new claims, however, explicitly exclude this peptide. The courts have long held that amendments to claims to specifically exclude prior art species from a claimed genus is proper under the patent laws (*see, e.g., In re Johnson and Farnham* 194 USPQ 187 (CCPA 1977). In light of the above, applicants believe the present rejection should be withdrawn.

35 U.S.C. §103.

The rejection of the claims as being obvious over Falk *et al. Nature* 351:290 (1991) is respectfully traversed. The rejection is apparently based on the presumed contents of a composition containing a large mixture of unsequenced peptides eluted from A2.1 molecules. According to the Examiner, such a mixture ***might*** contain peptides useful in the claimed methods. The Examiner's position is apparently based on the assumption that a disclosure

that peptides can be eluted from an MHC molecule is the same as disclosure of peptide sequences or a peptide binding motif. Applicants respectfully disagree.

It is well settled that the teachings of a prior art reference must be considered in their entirety. Moreover, the prior art must be considered in a manner consistent with its interpretation by one of skill at the time of the invention.

The present claims are directed to methods of using peptides having certain defined structural features that are nowhere disclosed or suggested in the cited reference. For instance, with regard to claim 19, the Examiner must show what in this reference would lead one of skill to make peptides having a motif in which the second position from the N-terminus is the amino acids I, V, A or T; and the C-terminus is V, L, I, A or M. The Examiner provides no reasoning or evidence to show why one of skill would select peptides having these features from the large collection of peptides that can be eluted from an MHC preparation. In the absence of a showing of what in particular in this reference leads one of skill to the peptides recited in the claimed methods the rejection is improper and should be withdrawn.

Moreover, the Falk *et al.* paper actually ***teaches away*** from the claimed methods because they teach that peptides with a completely different motif (set forth in Table 4) are good binders and hence immunogenic. Thus, one of skill reading this reference, at the time of the invention, would prepare peptides completely distinct from those used in the claimed methods.

Applicants respectfully submit that the Falk *et al.* paper when properly read as it would have been understood by one of skill in the art at the time of the invention, would not lead such a person to the claimed invention. In the absence of a showing why one of skill would be motivated to make peptides with a motif nowhere disclosed in this paper the rejection is improper and should be withdrawn.

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (415) 576-0200.

Respectfully submitted,

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